MULTIPLE NEUROGENIC EXTRACRANIAL TUMORS. CLINICAL, MRI FEATURES, AND DIAGNOSTIC DIFFICULTIES

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ABSTRACT

A case of multiple neurogenic tumors is presented. A native MRI (head and cervical spine) identified multiple bilateral tumors in the intraorbital space and cervical tumors. Based on the clinical course, imaging features and diagnosis criteria a possible diagnosis of schwannomatosis was made. Further investigations are needed for a precise diagnosis. This case presents discrepancies between the clinical presentation (paucity of symptoms) and imaging findings. A careful follow-up and surgical treatment is needed, in order to prevent the mass effects of these tumors.

Key words: neurofibromatosis, schwannomatosis

INTRODUCTION

The neurogenic extracranial tumors represents a small part of clinical pathology, and a rare situation. Among these, neurofibromatosis and schwannomatosis represents genetic conditions that share the predisposition to development of tumors of the nerve sheath. Two forms of neurofibromatosis have been recognized. The third form of these tumors is represented by schwannomatosis which is a non-neoplasic proliferation of Schwann cells that is characterized by the development of multiple peripheral schwannomas in the absence of other diagnosis features of NF2 (notably, vestibular scwannomas are not present). The true incidence is difficult to be determined, because the histopathologic examination is needed for precise diagnosis. Schwannomas may arise in association with any peripheral nerve in the head and neck. Other less common location may involve the anatomical region of the orbit (Love, Rose). The paper presents a clinical case with unusual location of peripheral nerve tumors which presents differential diagnosis difficulties.

CASE PRESENTATION

In October 2012, a 57 year old woman presented to the Neurology Department (Rehabilitation Hospital), for low back pain which has progressed over several weeks. Family history revealed a stroke (mother deceased by stroke), but no brain tumors or other locations tumors. Her medical history revealed hypertension, right kidney hypoplasia, chronic gastritis, Raynaud syndrome and hysterectomy for fibromatous uterus. 2 years previous, she developed cervical pain that brought her to the physician. The MRI examination concluded that the diagnosis is of neurofibromatosis. Her current medication contains antihypertensive drugs, antiplatelet therapy and calcium channel blocker (cinnarizine) for vertigo.

On general clinical examination she was found to be obese (body mass index – 28.5), arterial pres-

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sure of 140/80 mmHg. A Skin peduncular fibroma on the right arm and verrucous nevus in right axillary region were found. On neurological examination there was found a painless visual loss in the left eye, diminished osteotendinous reflexes in upper limbs (1+), subjective left arm paresthesias, objective hypoestesia (L4-L5-S1 territory). Other components of neurological clinical examination were normal.

Laboratory tests were normal. She was referred to the ophthalmologist for visual loss and to the cardiologist for hypertension treatment.

Diagnosis work-up

On ophthalmological examination there was found a decrease in distance visual acuity to 0.4 on the left eye (Snellen chart examination). On the right eye visual acuity was normal without refractive error correction. After optic correction the visual acuity was 0.9 (with spheric +1 lens correction; no more correction was useful). No extraocular muscle dysfunctions were found and the patient did not complain of ocular pains, nor diplopia. The structure of the iris was normal (there were no Lisch nodules on iris structure on slit lamp examination). On ophthalmoscopic and slit lamp examination cortical lens opacities were found (no posterior subcapsular lens opacities nor cortical lens opacities were present). These lens opacities are typically age-related cataract. The lens opacities were classified according to Lens Opacities Classification System III (Chylack, 1993). No retinal mass or other retinal abnormalities were found on ophthalmoscopic examination. Intraocular pressure was normal.

Because of clinical symptoms and based on neurological examination, the X ray examination of lumbar and cervical spine was indicated. On lumbar spine X ray examination minimal spondylosis changes were found. On cervical spine CT examination, 2 hypodensity tumoral masses were found (posterior to right sternocleidomastoid muscle and anterior to the trapezius muscle). The tumoral masses had clear limits and were 13 mm and 9 mm in diameter respectively. On ultrasound examination the same 2 masses were found. No vascularisation on Doppler examination was associated with these tumors. No structural changes of surrounding tissues were found.

Diagnosis consideration for decrease of visual function was made (Table 1).

TABLE 1. *Differential diagnosis for decrease in monocular visual function according to patient's age and clinical status*

Condition	Types	Features
Lens opacities	Cortical cataract Nuclear cataract	No ocular pain Insidious onset Distance visual acuity decreasing
Ischemic optic neuropathy	Non-arteritic ischemic optic neuropathy Arteritic ischemic optic neuropathy	No ocular pain Disc swelling ± nerve fiber layer hemorrhages
Inflammatory optic neuropathy Retinitis Vitreitis	Sjogren syndrome ± other autoimmune disease manifestation Sarcoidosis Paranasal sinusitis Bartonella infection Toxoplasmosis Lyme disease Cytomegalovirus Syphilis Tuberculosis	Disc swelling Retinal exudates Vitreous inflammation (vitreitis)
Glaucomatous causes	Chronic glaucoma Acute angle closure glaucoma	Optic disc cupping Elevated intraocular pressure Pain and scleral injection in acute angle closure glaucoma
Retinal causes (vascular)	Retinal artery occlusion (RAO) Retinal venous occlusion (RVO)	Retinal whitening (RAO) Retinal hemorrhages ± disc swelling (RVO)
Compression (orbit/ prechiasmatic optic nerve)	Lymphoma Leukemia Optic nerve glioma Metastasis Meningioma or other orbit/intracranial tumor	Slowly progressive visual loss Optic disc swelling or optic nerve atrophy

Based on the previous diagnosis of neurofibromatosis, decrease of visual function of the left eye and superior limb paresthesias and hypoestesias, a head and cervical spine MRI was indicated.

The MRI examination was made. The patient was tested for paramagnetic contrast agent (gadolinium) and type I hypersensitivity was found.

The native head MRI examination revealed multiple masses presence. Both orbits contain two well circumscribed, encapsulated, ovoid shaped masses. In T1-weightened images they revealed hypointensity, and in T2-weightened images they revealed hyperintensity. In the right orbit one of the masses is in contact with the optic nerve. There are more masses with the same MRI characteristics that were found in the retropharingeal space (bilaterally). The sizes of these masses are between 9.2/11.3 mm (the small one) to 12.8/39.6 mm (the bigger one). The

target sign was present for retropharingeal space tumors (T2-weightened images). Internal auditory canal contains no tumors (Fig. 1, 2). Leukoaraiosis lesions were also revealed by head MRI.

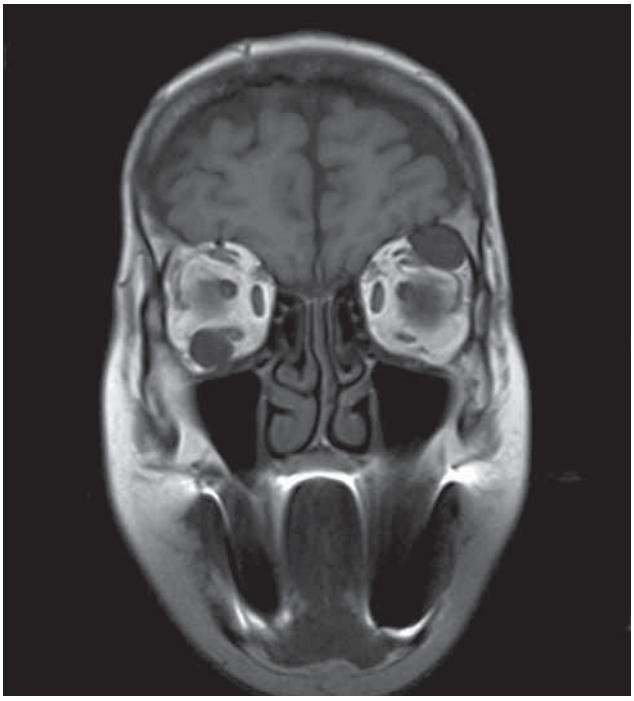

FIGURE 1. *Head MRI (native) – T1-weightened image in coronal section with bilateral orbital tumors (hypointense signal)*

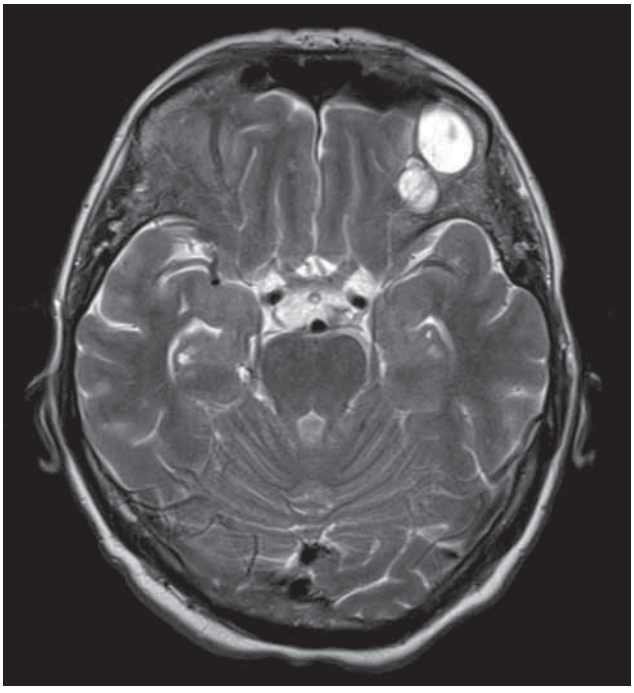

FIGURE 2. *Head MRI – T2-weightened image in axial section – 2 hyperintense masses in left orbit*

The native cervical MRI examination showed multiple masses wth the same T1 and T2-weightened characteristics. The masses are present at the following levels: spinal nerves levels (C2, C5, C6 bilaterally), a right vagus nerve mass, a sympathetic chain mass (at T1 level), a right laterocervical mass (on the lateral side of anterior scalen muscle). On the internal side of the common carotid artery there is one ovoid mass with the presence of target sign on T2-weightened images. The sizes of these masses are between 8/12 mm (the small one) to 22.7/27 mm (the bigger one) (Fig. 3).

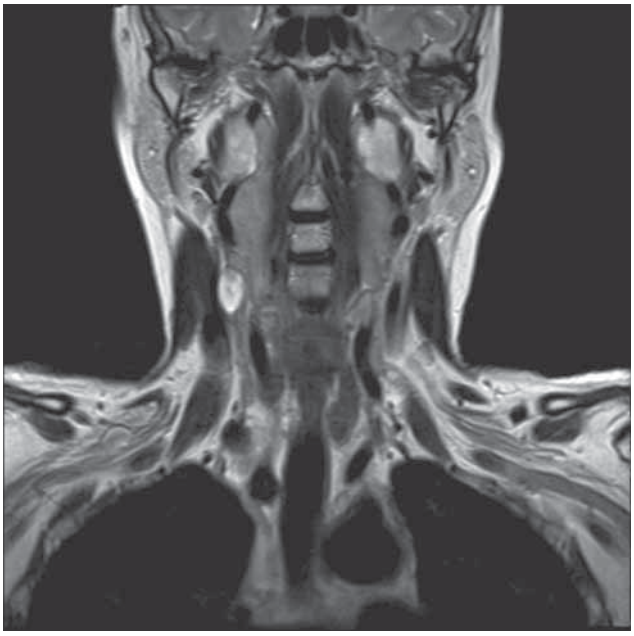

FIGURE 3. *Cervical spine MRI – T2-weightened image in coronal section – multiple masses with presence of target sign (along the vagus nerve bilateral)*

Lumbar spine cord MRI examination revealed no tumors.

Based on clinical course, history and MRI findings a possible diagnosis of schwannomatosis diagnosis was made. Type 1 neurofibramotosis (NF1) was excluded because there were no "cafe au lait spots" on the skin, nor cutaneous neurofibromas, Lisch nodules, skin fold freckling or optic nerve glioma. Diagnosis criteria for type 2 neurofibromatosis (NF2) and schwannomatosis was very important for diagnosis assumption (Table 2, 3).

TABLE 2. *Diagnosis criteria for NF2 – Manchester Clinical Diagnostic Criteria (Warner TT, Neurogenetics)*

A. Bilateral vestibular schwannoma
B. First degree family relative with NF2 and unilateral vestibular schwannoma or first-degree relative with NF2 and any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lens opacities
C Unilateral vestibular schwannoma and any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lens opacities
D. Multiple meningiomas and unilateral vestibular schwannoma or any two of: schwannoma, glioma, neurofibroma, posterior subcapsular lens opacities

TABLE 3. *Diagnosis criteria for schwannomatosis (MacCollin, 2005).*

Definite	Possible
Age > 30 years and two or more non-intradermal schwannomas, at least 1 with histologic confirmation and no evidence of vestibular tumor on MRi scan and no known constitutional NF2 mutation. OR One pathological confirmed non-vestibular schwannoma plus first degree relative who meets above criteria	Age < 30 years and two or more non-intradermal schwannomas, at least one with histologic confirmation and no evidence of vestibular tumor on MRI sc and no known constitutional NF2 mutation. OR Age > 45 years and two or more non-intradermal schwannomas, at least one with histologic confirmation and no symptoms of 8th nerve dysfunction and no constitutional NF2 mutation OR Radiographic evidence of non-vestibular schwannoma and first degree meeting criteria for definite schwannomatosis.

DISCUSSION

We present a clinical case observed at the Department of Neurology in the Rehabilitation Hospital who had particular clinical features due to discrepancies between cranial MRI findings and clinical symptoms (paucity of symptoms). There are few examinations that guided us toward the possible diagnosis: the native MRI, cervical spine CT examination and ultrasound soft tissue examination of the neck region. Based on these examinations, clinical presentation and taking into account of the differential diagnosis there is a possible diagnosis of schwannomatosis. The fulfill criteria for NF2 and schwannomatosis is difficult to be defined in most of patients, therefore the diagnosis is difficult. Other authors considered the schwanomatosis diagnosis (based on MRI findings) when multiple masses in relationship with peripheral nerves were found (Surov).

Schwannomatosis is a very rare disease which presents typically encapsulated, slow-growing tumors. They can occur in any location and at any age (most common between 20 to 50 year-old age group) (Delfini). Orbital schwannomas are infrequent, representing only 1% of orbital tumors (Capps). The particularity of this case is that, despite of the presence of orbital tumors which have a considerable volume, there are just a few ophthalmological symptoms (a slight acuity decrease which it possibly connected to the presence of cortical cataract). There were no mass effects (proptosis, optic nerve compresion, pain or diplopia). This fact suggests that there was a slow growing of the orbital tumors which is an important feature for diagnosing schwannomatosis. There are few orbital schwannomatosis cases reported in literature, therefore the clinical course of these tumor locations is poorly understood (Kron). Regarding the spinal localization of tumors, schwannomas represent the most frequent tumor lesions of the spine with prevalence for the cervical-inferior tract and the dorsolumbar passage. The surgical removal of these tumors is the main treatment when pain occurs (Conti).

Definitive diagnosis of schwannomatosis requires pathological demonstration or genetic testing. The patient refused the biopsy (because of paucity of symptoms). The only future possible test is the genetic test. Germline mutation in the SMARCB1 gene (c.233-1G >A and c.207_208 dupTA mutation). These mutations cause familial schwannomatosis, which is an autosomal dominant condition that predisposes individuals to develop different numbers of schwannomas (Melean, Smith) It is also possible to produce sporadic cases of schwannomatosis or multiple meningiomas (preferentially cranial meningiona located at falx cerebri) (van der Munckhof P). The case presented in this paper does not meet the MRI diagnosis criteria for meningioma (Scott).

According to the histopathological examination, schwannomas are characterized by the presence of specific hypercellular areas (Antoni type A areas), with frequent nuclear palisading arrangements (Verocay bodies), interspersed with less dense reticular areas (Antoni type B areas) with myxoid tissue and more water content. The target sign (biphasic signal intensity on T2-weighted images showed peripheral high intensity and central low intensity -) was present. The target sign is one of the characteristic imaging findings in schwannomas that distinguishes it from other soft tissue tumors. The target sign was defined as the biphasic or triphasic pattern on MRI, and the sign correlated with macroscopic and microscopic findings – microscopic patterns of central Antoni A and peripheral Antoni B cells. The specificity of the target sign in schwannoma was 100% and the sensitivity was 59%; therefore, the target sign was characteristic of and helpful for the diagnosis of schwannomas (Koga H, 2007; Scott W, 2009). The patient presents this specific target sign on head and cervical spine MRI examination, which was very useful in diagnosis guidance.

Even though schwannomatosis and NF2 are clinically, histopathologically, and genetically distinct, there is an overlap in their presentation and phenotype. For example, a sporadic patient may initially presents with multiple non-vestibular schwannoma, suggesting a diagnosis of schwannomatosis, and later a bilateral vestibular schwannoma develop, establishing the diagnosis of NF2 instead. The genetic test for NF2 does not clarify the diagnosis in all cases, because commercially available NF2 analysis is not able to detect the NF2 mutation in 33-45% of cases (Mac Collin). Therefore, the genetic test for NF2, in order to exclude the NF2 diagnosis has some limits (MacCollin, 2003).

CONCLUSION

We presented a clinical case which demonstrated the challenge in extracranial tumor diagnosis in absence of histopathological diagnosis and genetic tests. Additional clinical information and further examinations may aid the differential diagnosis in this clinical case. If the diagnosis is not clarified, the patient should be followed until the disease reveals more symptoms. For this clinical case, careful monitoring is needed before the tumors' sizes become problematic. Surgery remains the main treatment for schwannomas when the mass effect is present.

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